Advances in the management of hepatorenal syndrome

ALEX MYINT MD
Objectives

- Define acute kidney injury (AKI) and hepatorenal syndrome (HRS)
- Discuss treatment strategies in the management of HRS
  - Emphasis on role of terlipressin
- Review strategies to prevent HRS
Defining AKI

- Increase in serum creatinine >0.3mg/dL in 48 hours or >50% increase in creatinine within 7 days\(^1\)
- Common in patients with decompensated cirrhosis\(^2\)
- Associated with poor prognosis

Causes of AKI in cirrhosis

- Infection
- Hypovolemia
- HRS
- Parenchymal

Martin-Llahi et al. Gastroenterology. 2011
Hepatorenal syndrome

- Clinical syndrome resulting in AKI in patients with cirrhosis in the absence of hypovolemia or significant abnormalities in kidney histology

- Diagnostic criteria
  - Cirrhosis with ascites
  - Presence of AKI
  - No response to diuretic withdrawal and volume expansion
  - Absence of shock or other nephrotoxic insult
  - No signs of structural kidney disease

Current nomenclature

HRS-AKI
- Previously known as type 1 AKI
- Definition previously described
- Emphasis of this talk

HRS-CKD
- Previously known as type 2 HRS
- Slower progression than HRS-AKI
- Tends to occur in those with refractory ascites
- eGFR < 3 months in absence of other cause

Nadim and Garcia-Tsao. NEJM. 2023.
Why HRS happens

Bleeding → Bacterial translocation → ↑ Intrahepatic resistance

SBP, sepsis → ↑ Proinflammatory cytokines → Splanchnic and systemic vasodilatation

Infection, sepsis, LVP, vasodilators

Bleeding, volume depletion (diuretics, diarrhea) → ↓ Effective arterial blood volume

Activation of neurohumoral systems
- RAAS, sympathetic nervous system, arginine-vasopressin system

- Sodium retention
- Ascites

- ↑ Sodium and water retention
- Refractory ascites ± hyponatremia

- Renal vasoconstriction
- ↓ Renal blood flow

↑ Cardiac output
- Cirrhotic cardiomyopathy
- ↓ Cardiac output

HRS-AKI

Nadim and Garcia-Tsao. NEJM. 2023.
HRS-AKI Management Strategies

- Terlipressin
- Norepinephrine
- Midodrine/Octreotide
- Renal replacement therapy
- TIPS?
- Transplantation
Goals in HRS-AKI therapy

- Improve renal perfusion
- Avoid additional nephrotoxic insults
- Albumin is a part of all regimens
- Treat until resolution
- Bridge to transplant (if possible)

Terlipressin

- Vasopressin analogue with vasoconstrictor activity in the splanchnic and systemic vasculature
- Given as IV infusion for treatment of HRS-AKI
- Used in Europe as 1st line treatment of HRS-AKI, recently approved in US

Wong et al. NEJM. 2021.
CONFIRM Trial

- RCT of 300 patients with decompensated cirrhosis and HRS-AKI
  - Randomized 2:1 terlipressin/albumin vs placebo/albumin
- Treatment associated with increased HRS-AKI reversal, less need for RRT, and short-term survival (10 days after treatment)
- No improvement in longer term survival

Table 2. Primary and Four Secondary End Points Included in Multiplicity Adjustment.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Terlipressin</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point of verified reversal of HRS†</td>
<td>number/total number of patients (percent)</td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Clinical success</td>
<td>63/199 (32)</td>
<td>17/101 (17)</td>
<td></td>
</tr>
<tr>
<td>Clinical failure</td>
<td>121/199 (61)</td>
<td>81/101 (80)</td>
<td></td>
</tr>
<tr>
<td>Competing event‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>10/199 (5)</td>
<td>2/101 (2)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>5/199 (3)</td>
<td>0/101</td>
<td></td>
</tr>
</tbody>
</table>

HRS reversal with no renal-replacement therapy through 30 days

| Clinical success | 68/199 (34) | 17/101 (17) | 0.001 |
| Clinical failure | 116/199 (58) | 80/101 (79) | |
| Competing event‡ | | | |
| Liver transplantation | 10/199 (5) | 3/101 (3) | |
| Death | 5/199 (3) | 0/101 | |

Wong et al. NEJM. 2021.
Using terlipressin

- Give 0.85mg IV every 6 hours x 3 days
- Reassess on day 4
  - If <30% improvement, may increase to 1.7mg every 6 hours
  - If >30% improvement, continue 0.85mg every q 6 hours
  - If at baseline, discontinue
- Continue until creatinine <1.5mg/dL x 24 hours or 14 days total

- Assess ACLF grade and volume status prior to treatment
- Oxygen saturation monitoring required
  - Do not start if SpO2 <90%
  - Patients require continue pulse oximetry while on treatment
- Treatment discontinuation may be necessary if ischemia, respiratory failure, or volume overload
Contraindications

- Hypoxia (SpO2<90%)/respiratory failure
- Evidence of ischemia
- Terlipressin may worsen these
- ACLF grade 3 associated with higher risk of respiratory failure
- Creatinine >5 unlikely to benefit

Additional adverse reactions

- Abdominal pain
- Nausea
- Respiratory failure
- 12% had adverse events that led discontinuation

Terlipressin prescribing information
Norepinephrine

- Titrated dose to achieve >10mmHg increase in MAP
- Use when terlipressin not available/contraindications
  - May be as effective as terlipressin
- Logistical challenge related to need for ICU bed

An ounce of prevention is worth a pound of cure.

Benjamin Franklin
Strategies to Prevent HRS-AKI

- Avoid nephrotoxic medications in at risk patients (NSAIDs, ACE inhibitors, ARBs)
  - Window period for beta blockers
  - Judicious use of IV contrast
- Avoid volume depletion
- Albumin with large volume paracentesis and during episodes of SBP
- Provide antibiotics during GI bleed or as SBP prophylaxis, if indicated

Nadim and Garcia-Tsao. NEJM. 2023.
Takeaway points

- AKI is common in patients with decompensated cirrhosis
- HRS-AKI is a rapidly progressive condition associated with high mortality
- Vasoconstrictor therapy to raise MAP (and renal perfusion) can help reverse HRS-AKI but urgent transplant evaluation should be considered
- Terlipressin was recently approved to treat HRS-AKI
- Prevention of HRS-AKI is important